Predictors of blisters in patients with acute compartment syndrome

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Research Article

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Abstract

Introduction: Blisters, one of the most common complications of orthopedic trauma, can result in surgery delay and increase the risk of infection. This study aimed to identify the risk factors for blisters in patients with acute compartment syndrome (ACS).

Methods: We gathered data from two hospitals' 206 ACS patients from November 2013 to January 2021. Patients were divided into the blister group (BG) and the control group (CG) according to whether they had blisters or not. We used univariate analysis, logistic regression analysis, and receiver operating characteristic (ROC) curve analysis to determine the demographics, comorbidities, and admission laboratory tests.

Results: In our research, the incidence of blisters was 21.8 % (45 of 206). Univariate analysis showed that numerous factors were releated to the formation of blisters. According to logistic regression analysis, patients who developed ACS in the winter or spring (p = 0.007, OR = 2.690, 95% CI (1.308 to 5.534), patients who received a referral (p = 0.009, OR = 4.235, 95% CI (1.432 to 12.527), and patients with higher PLR (p = 0.036, OR = 1.005, 95% CI (1.000 to 1.009) were independent risk factors for blisters. In addition, a history of drinking (p = 0.039, OR = 0.027, 95% CI (0.046 to 0.927)) represented a protective factor for the formation of blisters in these patients. ROC curve analysis revealed that 138.17 was the cut-off value of PLR to predict the blister. Furthermore, the combination of seasonal factors, PLR, and referral had the highest diagnostic accuracy.

Conclusions: Our findings identified seasonal factors, referral, and patients with higher PLR as independent risk factors while a history of drinking as protective factor for blisters in ACS patients, allowing us to individualize the evaluation of the risk of blisters in order to perform early targeted therapies.

Introduction

Acute compartment syndrome (ACS) results from fractures or other trauma that occurs inside a closed fascial compartment [1,2]. The incidence of ACS is 3.1 per 100,000 people per year, with males being afflicted 10 times more commonly than women [3, 4]. The consequences of delayed or improper treatment may be catastrophic, including loss of function or even death [5]. The pathophysiological mechanism underlying ACS is postprocedural reperfusion-induced edema, which may result in elevated compartment pressure and tissue necrosis [6]. The leg and the forearm are the areas of the body most commonly affected by ACS [3, 4]. Likewise, these regions are often accompanied by skin blisters.

Approximately 2.9% of hospitalized patients have blisters on their skin, which are associated with various common disorders, including burns, cupping, and fractures [7-11]. Blisters are typically caused by high-energy orthopedic trauma to vulnerably exposed regions of the body, such as the ankle, wrist, elbow, and foot, where skin clings strongly to bone and subcutaneous fat cushioning is limited [12]. It is believed that the occurrence of blisters following fractures can cause certain problems for clinicians, including a

postponement of surgery and an increased risk of infection [13]. Several prior studies have reported the formation of blisters [14]. During the inflammatory phase, edematous soft tissue causes a rise in interstitial pressure. Consequently, filtration pressure rises, resulting in decreased cohesiveness between epidermal cells and facilitating fluid transfer into the blister. In addition, increased colloid pressure contributes to blister development. This pressure, which in epidermal or subepidermal fissures stimulates fluid flow into the crack, is an additional element in blister formation. However, to our knowledge, few studies have focused on the predictors of blisters in patients with ACS. To comprehensively investigate factors related to the prevalence of blisters in these patients, we retrospectively reviewed 206 patients with ACS and identified their blister risk factors.

Materials And Methods

Ethics Statement

ACS patients diagnosed and treated between November 2013 and January 2021 at the 3rd Hospital of Hebei Medical University and Baoding No. 1 Central Hospital were included in our study. In line with the ethical rules of the Helsinki Declaration from 1964, we got permission from the institutional review boards of these two hospitals. (NCT04529330, S2020-022-1) (2022116).

Patients

This retrospective study was carried out at the 3rd Hospital of Hebei Medical University and Baoding No.1 Central Hospital, both of which were tertiary hospitals with a level I trauma center. Patients with traumatic ACS and those with complete medical records could be included in this study. The exclusion criteria were: (1) patients with non-traumatic ACS; (2) patients who developed blisters prior to admission; (3) patients younger than 18 years old; and (4) patients with open fractures. (Figure 1)

According to the above criteria, 206 patients (180 men and 26 women) were enrolled in this study. Based on whether these individuals had blisters or not, we divided them into two groups: the blister group (BG) and the control group (CG). All patients received cryotherapy and passive limb elevation during admission and hospitalization to prevent further soft tissue injury or blister formation. Ice could inhibit the inflammatory response and thereby reduce soft tissue edema by decreasing soft tissue temperature [15]. Besides, elevating the limb reduces soft tissue edema by assisting venous and lymphatic drainage [16]. Despite the above-mentioned preventive measures having been adopted by all patients included in this study, the rate of blisters remained high (21.8%). Once the blisters appeared and caused great pain to the patients, experienced surgeons would incise the base of the blister with a blade in two to four locations to aspirate the fluid and cover it with a sterile dressing. Dressings would be changed every few days until the base was re-epithelialized, which could take more than one week. In the present research, 160 patients experienced blister fluid extraction, while 46 patients did not.

In this study, we analyzed patients' demographics, comorbidities, and admission laboratory tests. Age, gender, BMI (24, 24-28, and > 28 kg/m2), injury mechanism (car crash injury, fall injury, crush injury, and

hurt by a crashing object), ASA score (American Society of Anesthesiologists score), seasonal factors, referral or not, smoking, alcohol, time from injury to admission, and whether or not a dehydrating agent was used were all included in the demographic information. The ASA score was classified into two groups: grades 1-2 and grades 3-4. The seasons were grouped into two categories: summer and autumn, while winter and spring were combined. Comorbidities included arrhythmia, diabetes, hypertension, coronary heart disease, hypoproteinemia, anemia, and cerebral infarction. At the time of admission, we also looked at basophil (BAS), eosinophil (EOS), hematocrit (HCT), hemoglobin (HGB), immature (IMM), lymphocyte (LYM), mean corpuscular hemoglobin concentration (MCHC), monocyte (MON), mean platelet volume (MPV), neutrophil (NEU), platelet (PLT), red blood cell (RBC), white blood cell (WBC), activated partial thromboplast (APTT), fibrinogen (FIB), international normalized ratio (INR), prothrombin time(PT), thrombin time (TT), albumin (ALB), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine transaminase (ALT), Calcium (Ca), K, Na, Mg, P, Cl, globulin (GLOB), cholinesterase (CHE), creatine kinase (CK), creatinine (CREA), direct bilirubin (DBIL), glucose (GLU), lactic dehydrogenase (LDH), osmotic pressure(OSM), triglyceride (TG), total cholesterol (TC), total protein(TP), total carbon dioxide (TCO2), ureophil (UREA), and uric acid (UA). We also collected and calculated several ratio metrics, such as NLR, MLR, and PLR. NLR/MLR were obtained by dividing the neutrophil/monocyte count by the lymphocyte count, and PLR was computed by dividing the platelet count by the lymphocyte count.

Statistics

In this research, we utilized SPSS (version 25.0, SPSS Inc., New York, USA), and a p-value of 0.05 was considered statistically significant. The Shapiro-Wilk test was used to determine the normality of continuous variables. When normality is fulfilled, these variables are expressed as mean±SD (standard deviation) and used in a t-test. However, if not, we would use the median and interquartile range (IQR), and the Mann-Whitney U test is used to perform statistical analysis between groups. We compare the between-group difference for count data, expressed as a number and its percentage, using the Chi-square and Fisher's exact tests. Additionally, we used binary logistic regression analysis to find the best prognostic indicator for patients with ACS.

When the Youden index (sensitivity+specificity-1) reached its maximum, we routinely used ROC (receiver operating characteristic) analysis to determine the optimal cut-off values for continuous variables, such as PLR. These indexes were classified as low versus high risk because of the cut-off value. The area under the ROC curve (AUC) was used to determine the diagnostic ability, which ranged from 0 to 100%, with more area meaning better ability.

Result

This study enrolled 206 patients, including 180 men and 26 women. Among these 206 patients, 160 experienced blister fluid extraction, while 46 did not. The blistering rate in ACS patients was 21.8%, with 45 patients having blisters and 161 not.

Table 1 showed no statistically significant differences in age, gender, BMI, injury mechanism, time from injury to admission, multiple fractures, smoking history, ASA classification, and using a dehydrating agent or not between these two groups (all $p > 0.05$). However, we have observed significant differences between the BG and CG in seasonal factors ($p = 0.007$), referral ($p = 0.024$), and patients with a history of drinking ($p = 0.020$). According to this table, there were significant differences in the seasons of blister formation in ACS patients, with blisters more likely to occur in the winter and spring. Regarding referrals, the BG had a higher proportion than the CG. However, patients in the CG had a higher probability of having a history of alcohol consumption compared to the BG.

Table 2 compared the comorbidity data between the two groups. However, no significant differences were found between the two groups regarding comorbidities, including arrhythmia, coronary heart disease, diabetes, hypertension, cerebral infarction, hypoproteinemia, and anemia (all $p > 0.05$). Table 3 summarized the results of the laboratory findings between the BG and the CG. The levels of MLR ($p = 0.011$) and PLR ($p = 0.048$) were significantly higher in BG than in CG. In addition, the level of TC ($p = 0.027$) was significantly higher in BG than in CG. However, these two groups had no significant differences in other laboratory results (all $p > 0.05$).

As shown in the logistic regression analysis, patients who developed ACS in the winter or spring ($p = 0.007$, OR = 2.690, 95% CI (1.308 to 5.534)), patients who had a history of referral ($p = 0.009$, OR = 4.235, 95% CI (1.432 to 12.527)), and patients with a higher PLR ($p = 0.036$, OR = 1.005, 95% CI (1.000 to 1.009)) were independent risk factors for blister in ACS patients. Furthermore, a history of alcohol ($p = 0.039$, OR = 0.207, 95% CI (0.046 to 0.927)) represented a protective factor for the formation of blisters in these patients. (Table 4).

The predictors revealed by the ROC curve analysis were shown in Figure 2, which showed that seasonal factors, PLR, and referral were independent predictors of blisters, with 138.17 being the cut-off value for PLR. Figure 3 depicted the AUC for seven different indexes: seasonal factors alone ($p = 0.009$, AUC area = 0.610, 95% CI (0.540 to 0.667)), PLR alone ($p = 0.037$, AUC area = 0.597, 95% CI (0.526 to 0.664)), referral alone ($p = 0.006$, AUC area = 0.581, 95% CI (0.511 to 0.649)), seasonal factors+PLR ($p=0.002$, AUC area=0.654, 95%CI (0.585 to 0.719)), seasonal factors+referal ($p<0.001$, AUC area=0.660, 95%CI (0.591 to 0.724)), PLR+referal ($p=0.001$, AUC area=0.654, 95%CI (0.585 to 0.719)), seasonal factors+PLR+referal ($p<0.001$, AUC area=0.691, 95%CI (0.623 to 0.753)). After combining various factors, the AUC area increased significantly, indicating a superior diagnostic value. The diagnostic value of seasonal factors+PLR+referal was highest when the area beneath the receiver operating characteristic curve was 0.691. (Figure 4)

Discussion

ACS is a complication of a fracture or other trauma that occurs within a closed fascial compartment [1,2]. Postprocedural reperfusion-induced edema is the pathophysiological process causing ACS, which may lead to elevated compartment pressure and tissue necrosis [6]. A delayed diagnosis may result in

irreversible nerve and muscle damage, amputation, or even death [5]. Blisters are the consequences of the increasing pressure in the compartment, which commonly occur in the leg and forearm impacted by ACS [3, 4]. Blisters have impacted 2.9% of hospitalized patients and are often caused by high-energy orthopedic injuries to areas of the body where skin adheres tightly to bone and subcutaneous fat is limited [12]. Clinicians may face various problems caused by blisters, such as delayed surgery time and an increased risk of infection [13]. Due to the high incidence and poor prognosis of blisters, it is essential to investigate its predictors and apply preventative measures. Although ongoing research has focused on the development of blisters [14], limited attention has been paid to the predictors of blister formation in ACS patients. To our knowledge, this is the first study to investigate the risk factors for blisters in patients with ACS.

In the present study, we found that the rate of blisters (45 of 206) was 21.8%. Several predictors were identified to be associated with blisters by using univariate analysis, including seasonal factors, referral, a history of alcohol, the level of TC, and higher MLR and PLR. According to logistic regression analysis, patients admitted in the winter or spring, patients with a referral history, and patients with a higher PLR were relevant predictors of blisters. ROC curve analysis revealed that 138.17 was the cut-off value for PLR for predicting the formation of the blister. Furthermore, the combination of seasonal factors, PLR, and referral had the highest diagnostic accuracy.

Our study reported an increased occurrence of blisters among patients with referrals. We also discovered that, compared with patients who first came to our hospital, those who experienced referral had a 4.235-fold increase in the risk of blisters. Not only did the referral increase the waiting time before hospitalization, but it also reflected that the patients had undergone repeated moves, multiple imaging and physical examinations. Before being admitted to our hospital, a number of patients in our research were referred multiple times to several other hospitals for the same imaging and physical tests. Throughout this procedure, there would inevitably be frequent patient transfers, repetitive motions of the fractured region, prolonged waiting times, and repeated evaluations at various medical facilities. These undoubtedly delayed early interventions, such as the use of dehydrant or ice to relieve soft tissue swelling, resulting in worsened soft tissue injury and edema. Previous research has demonstrated that the soft tissue damage caused by ACS is usually enough to cause soft tissue edema and inflammation, which in turn leads to dermal hypoxia and much more soft tissue damage [17]. This extra soft tissue damage may result in skin blistering and, in some circumstances, cutaneous and even muscular necrosis [18]. The above results were consistent with our study. Furthermore, Nelson et al. recommend early fracture reduction and stabilization to decrease the incidence of fracture blisters [19]. Frank et al. believed that the initial stage of fracture-related soft tissue damage therapy was immobilizing the broken limb as quickly as possible, ideally on the site of the accident, to avoid additional soft tissue injury [20]. The perspectives of the researchers, as mentioned above, were consistent with the findings of this research, reflecting that the occurrence of blisters in ACS patients was closely related to repeated referrals. Therefore, enhancing the capability of primary care hospitals, early temporary external fixation, and prompt information exchange between different referral hospitals are crucial measures to reduce blistering in ACS patients.

In our study, the level of PLR was much higher in BG than in CG. There was no previous research investigating the connection between PLR and blisters, but we can get valuable information from the perspective of trauma severity. Maria et al. suggested that ACS caused by fractures was related to the degree of energy release suffered at the moment of injury, with more energy release resulting in more severe soft tissue damage that may in turn worsen ACS [21]. In the meantime, some researchers believe that the degree of soft-tissue damage after fractures is directly associated with the occurrence of blisters [22]. Therefore, the blisters that develop in ACS patients were treated as a particular kind of fracture blister and were thought to indicate the severity of the trauma. The platelet-to-lymphocyte ratio (PLR) is becoming recognized as an indicator of systemic inflammatory response in fractures, malignant tumors, and polytrauma. [23-26] The previous study has shown that significant trauma often leads to increased platelet (PLT) activation and activity, initiating the coagulation cascade and immunological reactions [27]. Wang et al. [23] found that postoperative PLR seems to be a valuable biomarker that correlates strongly with the severity of surgery-related trauma in patients with bicondylar TPFs. The findings of the research mentioned above demonstrated that PLR is an indicator of the severity of the injury, and the severity of trauma is correlated with the emergence of blisters, demonstrating the relationship between blisters and PLR. Our findings indicated that PLR was a predictor of blisters in ACS patients, which was consistent with the above findings. In clinical work, with the prediction of PLR, there can be a reliable basis for forecasting the occurrence of blisters and implementing appropriate countermeasures for patients with ACS. Furthermore, we investigated the role of MLR, a valuable indicator of inflammation, in blister diagnosis. In univariate analysis, MLR was shown to be associated with blisters. However, it was not an independent risk factor based on logistic regression analysis.

In this research, seasonal factors were found to be an independent risk factor for the development of blisters in patients with ACS, with a higher incidence in the winter and spring. Shijiazhuang and Baoding are located in the north of China, where the average temperature in winter and spring could reach -3.0°C to 7.0°C. Seasonal changes are essentially changes in temperature, which might have an influence on fracture-related disorders. In previous studies, several researchers discovered a link between fracture and temperature. Cecilie et al. believed that cold ambient temperatures can increase the incidence of forearm and hip fractures, as well as post-hip fracture mortality [28]. Moreover, Kinga et al. found that the changes in fracture incidence throughout the observation time are related to the season (warmer versus colder) and the increase of mean temperature during the observation period [29]. This could be due to the cold weather requiring thicker and additional clothing, resulting in repeated movements due to the inconvenience of exposing the affected limb during the emergency examination. In addition to this, cold weather may have a negative impact on the patient's exposure to the external environment at the time of injury and during ambulance transport. Hypothermia could have a detrimental impact on trauma patients' metabolic and coagulation systems. Thermostasis may be maintained with simple interventions starting in the prehospital setting, such as passive external warming (covering the patient, away from the cold surroundings), active external warming (hot packs, reflective blankets), and core warming (warmed IV fluids) [30]. Despite the above approach, studies have also reported that 85% of the patients had a finger temperature below the comfort zone in the ambulance, and 44% felt the ambient temperature to be chilly.

There was a significant decrease in finger temperature between the first indoor test and the one performed in the ambulance. In prehospital care, exposure to the winter cold was common. Sick and injured patients respond rapidly to exposure to the cold by experiencing a decrease in finger temperature and pain from the cold. As a result, maintaining the patient at a comfortable temperature was critical. Further research is required to increase knowledge that may be used to improve prehospital care for patients who probably already suffer from cold weather [31]. The correlation between blisters and seasonal factors in this study's ACS patients requires that patients be kept warm at the time of injury and throughout transfer in the future. According to the current research findings, the evaluation of whether or not a patient had been exposed to cold offered some assistance in predicting the occurrence of blisters in ACS patients. This prediction provided a solid basis for our perioperative care and surgical planning, therefore preventing the waste of medical resources and the occurrence of unnecessary surgery and perioperative complications about blisters.

We also identified an indicator that acted as a protective factor against blisters. According to logistic regression analysis, patients with a drinking history performed a protective function in preventing blister development.Previous researchers have established a correlation between alcohol consumption and bone mineral density [32-34]. Patients with a history of alcohol consumption tended to have higher bone mineral density. Lower bone density was more likely to result in the development of comminuted fractures [34], which in turn caused significant soft tissue injury. As mentioned above, severe soft tissue injury was positively correlated with the appearance of blisters, which may explain the protective role of a drinking history in delaying the development of blisters.

Even though this is the first study to investigate the risk factors for blister development in patients with ACS, some limitations should be noted. First, because this was a retrospective analysis, several possible factors that may be related to blisters, such as surgical history, were only partly available. Second, owing to the small number of ACS patients, we did not perform a subgroup analysis based on the location of blisters, such as lower leg blisters or upper limb blisters. Third, similar to any other multivariate study, we could not incorporate all confounding variables, and residual confounding remains a concern.

In conclusion, univariate analyses indicated that seasonal factors, referral, MLR, PLR, and TC were associated with blisters, and logistic regression demonstrated that patients who developed ACS in the winter or spring, patients with referral, and patients with a higher PLR were independent predictors of blisters. We determined that 138.17 was the cut-off value of PLR to predict the blister. A drinking history was also discovered to be a significant protective factor for developing blisters. Our results offered a personalized risk assessment for blister formation in patients with ACS, enabling prompt and targeted interventions.

Abbreviations

ACS=acute compartment syndrome; ASA=American Society of Anesthesiologists; PLR=platelet to lymphocyte rate; MLR=monocyte to lymphocyte rate; NLR=neutrophil to lymphocyte rate; ROC=receiver

operating characteristic curve; AUC=area under the curve; BMI=body mass index; BAS=basophil; EOS=eosinophil; HCT=hematocrit; HGB=hemoglobin; IMM=immature; LYM=lymphocyte; MCHC=mean corpusular hemoglobin concentration; MCV=mean corpuscular volume; MON=monocyte; MPV=mean platelet volume; NEU=neutrophil; PLT=platelet; RBC=red blood cell; WBC=white blood cell; APTT=activated partial thromboplastin time; FIB=fibrinoge; INR=international normalized ratio; PT=prothrombin time; TT=thrombin time; ALB=albumin; ALP=alkaline phosphatase; AST=aspartate aminotransferase; ALT=alanine transaminase; Ca=calcium; GLOB=globulin; CHE=cholinesterase; CK=creatine kinase; CREA=creatinine; DBIL=direct bilirubin; GLU=glucose; LDH=lactic dehydrogenase; OSM=osmotic pressure; TG=triglyceride; TC=total cholesterol; TCO2=total carbon dioxide; TP=total protein; UREA=ureophil; UA=uric acid.

Declarations

Ethics approval and consent to participate: This retrospective study was approved by the Institutional Review Board of the 3rd Hospital of Hebei Medical University and Baoding No.1 Central Hospital (NCT04529330, S2020-022-1) (2022116) before collecting data. There is no need to write informed consent forms from patients because this is a retrospective study.

Consent for publication: Not applicable.

Availability of data and material: Yes

Competing interests: There is no competing interests

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Authors' contributions: YBL, SY and TW was responsible for study concept and writing the article. YRL, QD, LMW and LLM were responsible for screened the abstracts and reviewed the article. ZYH and JFG was responsible for reviewing and writing the article.

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Tables

Table1. Demographics data of patients with and without blisters

Characteristics	Blister group (n=45)	Non-Blister group (n=161)	*p*
Age, years	39.0 (30.0~54.8)	40.0 (28.5~51.0)	0.742
Gender, n (%)			0.503
male	38 (84.4%)	142 (88.2%)	
female	7 (15.6%)	19 (11.8%)	
Body mass index, kg/m2	24.5 (22.7~27.3)	24.5 (22.5~26.7)	0.774
24	16 (35.6%)	55 (34.2%)	0.975
24-28	22 (48.9%)	79 (49.1%)	
28	7 (15.6%)	27 (16.8%)	
mechanism of injury,n (%)			0.213
car crash injury	9 (20.0%)	35 (21.7%)	
Fall Injury	12 (26.7%)	20 (12.4%)	
crush injury	9 (20.0%)	46 (28.6%)	
hurt by a heavy object	5 (11.1%)	18 (11.2%)	
unknown trauma	10 (22.2%)	42 (26.1%)	
Seasonal factors			0.007*
Winter and spring	25 (55.6%)	54 (33.5%)	
Summer and fall	20 (44.4%)	107 (66.5%)	
Referral			0.024*
Yes	40 (88.9%)	117 (72.7%)	
No	5 (11.1%)	44 (27.3%)	
Time from injury to admission	6 (3.3~14.3)	6 (4~11)	0.859
multiple fracture, n (%)			0.681
Yes	27 (60.0%)	102 (63.4%)	
No	18 (40.0%)	59 (36.6%)	
Smoking history□n (%)			0.270
Yes	5 (11.1%)	29 (18.0%)	
No	40 (88.9%)	132 (82.0%)	

Alcohol history，n (%)			0.020*
Yes	2 (4.4%)	24 (14.9%)	
No	43 (95.6%)	137 (85.1%)	
Dehydrating agent or not, n (%)			0.272
Yes	104 (64.6%)	33 (73.3%)	
No	57 (35.4%)	12 (26.7%)	
ASA			0.320
1-2	38 (90.5%)	130 (84.4%)	
3-4	4 (99.5%)	24 (15.6%)	

Table2. Comorbidities data of patients with and without blisters

Comorbidities	Blister group (n=45)	Non-Blister group (n=161)	*p*
Arrhythmia, n (%)			0.516
Yes	0 (0.0%)	5 (3.1%)	
No	45 (100.0%)	156 (96.9%)	
Coronary heart disease, n (%)			0.708
Yes	2 (4.4%)	12 (7.5%)	
No	43 (95.6%)	149 (92.5%)	
Hypertension, n (%)			0.781
Yes	6 (13.3%)	19 (11.8%)	
No	39 (86.7%)	142 (88.2%)	
Diabetes, n (%)			0.338
Yes	0 (0.0%)	7 (4.3%)	
No	45 (100.0%)	154 (95.7%)	
Cerebral Infarction, n (%)			1.000
Yes	2 (4.4%)	6 (3.7%)	
No	43 (95.6%)	155 (96.3%)	
Hypoproteinemia, n (%)			0.871
Yes	6 (13.3%)	23 (14.3%)	
No	39 (86.7%)	138 (85.7%)	
Anemia			0.780
Yes	13 (28.9%)	50 (31.1%)	
No	32 (71.1%)	111 (68.9%)	

Table3. Laboratory results of patients with and without blisters

Laboratory results	Blister group (n=45)	Non-Blister group (n=161)	*p*
BAS	0.04 (0.01~0.08)	0.04 (0.01~0.07)	0.730
EOS	0.09 (0.02~0.16)	0.11 (0.05~0.17)	0.449
HCT	38.23 (33.95~43.13)	38.82 (34.58~43.47)	0.869
HGB	130.10 (114.40~145.15)	131.20 (117.35~148.00)	0.888
IMM	0.18 (0.04~0.20)	0.15 (0.05~0.19)	0.988
LYM	1.37 (1.06~1.66)	1.54 (1.06~1.90)	0.189
MCH	31.33 (30.25~32.49)	31.27 (30.08~32.21)	0.368
MCHC	337.43±10.79	337.82±9.94	0.816
MCV	92.77 (90.12~95.71)	92.34 (89.15~95.40)	0.337
MON	0.97 (0.62~1.17)	0.81 (0.57~1.07)	0.055
MPV	9.00 (8.09~9.94)	8.97 (7.88~9.81)	0.651
NEU	10.96 (7.92~15.76)	10.88 (6.89~13.22)	0.481
PLT	219.36±51.87	208.62±72.49	0.267
RBC	4.28 (3.70~4.72)	4.33 (3.71~4.84)	0.870
WBC	12.87 (10.16~18.14)	13.15 (9.55~16.50)	0.555
NLR	59.23 (45.29~81.99)	54.83 (37.62~77.61)	0.197
MLR	0.66 (0.53~1.04)	0.54 (0.38~0.84)	0.011*
PLR	164.97 (122.88~206.82)	137.32 (104.01~189.85)	0.048*
ALB	36.44 (33.53~40.60)	36.29 (35.55~42.35)	0.940
ALP	67.69 (56.00~70.00)	69.18 (56.00~70.10)	0.165
ALT	39.00 (21.50~48.21)	37.00 (24.00~50.02)	0.644
AST	63.00 (28.00~100.27)	48.00 (27.00~112.49)	0.913
Ca	2.08 (2.08~2.22)	2.09 (2.09~2.19)	0.089
CHE	6.61 (6.61~7.41)	6.63 (5.89~7.02)	0.518
CK	4965.41 (998.95~4965.41)	2993.25 (381.75~5347.68)	0.768
CL	104.48 (101.30~104.84)	104.26 (102.70~105.95)	0.466
CREA	68.16 (60.87~73.15)	68.09 (56.96~69.55)	0.098
DBIL	5.51 (3.47~6.89)	5.45 (3.50~5.98)	0.083

GLOB	22.22 (20.95~23.90)	22.23 (20.30~23.40)	0.318
GLU	8.90 (6.40~10.39)	9.00 (6.13~10.16)	0.362
K	3.92 (3.75~4.23)	3.92 (3.67~4.09)	0.139
LDH	615.31 (257.91~615.31)	628.00 (260.93~689.60)	0.269
Mg	0.83 (0.77~0.83)	0.82 (0.77~0.86)	0.373
Na	137.99 (135.79~138.80	137.79 (136.65~139.60)	0.638
OSM	270.83 (267.55~270.97)	270.29 (267.45~271.55)	0.184
P	1.11 (0.97~1.18)	1.11 (1.01~1.19)	0.082
TC	3.46 (2.83~4.08)	3.42 (3.05~3.65)	0.027*
TCO2	23.70 (21.71~25.00)	23.70 (22.52~25.80)	0.743
TG	1.32 (0.97~1.32)	1.31 (0.85~1.31)	0.165
TP	58.44 (57.60~67.05)	58.57 (54.15~65.16)	0.670
UA	313.00 (256.50~314.21)	318.99 (248.50~363.00)	0.088
UREA	5.53 (4.49~5.90)	5.48 (4.30~5.76)	0.105
APTT	29.38 (26.55~30.35)	29.56 (26.70~30.90)	0.696
FIB	2.77 (2.38~3.10)	2.77 (2.23~3.01)	0.733
INR	1.09 (1.02~1.13)	1.10 (1.02~1.14)	0.457
PT	12.40 (11.80~13.00)	12.57 (11.40~13.00)	0.488
TT	16.00 (14.10~16.73)	16.40 (14.45~17.25)	0.915

Table4. Binary logistic regression analysis of variables associated with blisters

Characteristics	OR	95%CI	*p*
Season	2.690	1.308 to 5.534	0.007*
Referral	4.235	1.432 to 12.527	0.009*
Alcohol	0.207	0.046 to 0.927	0.039*
PLR	1.005	1.000 to 1.009	0.036*

Figures

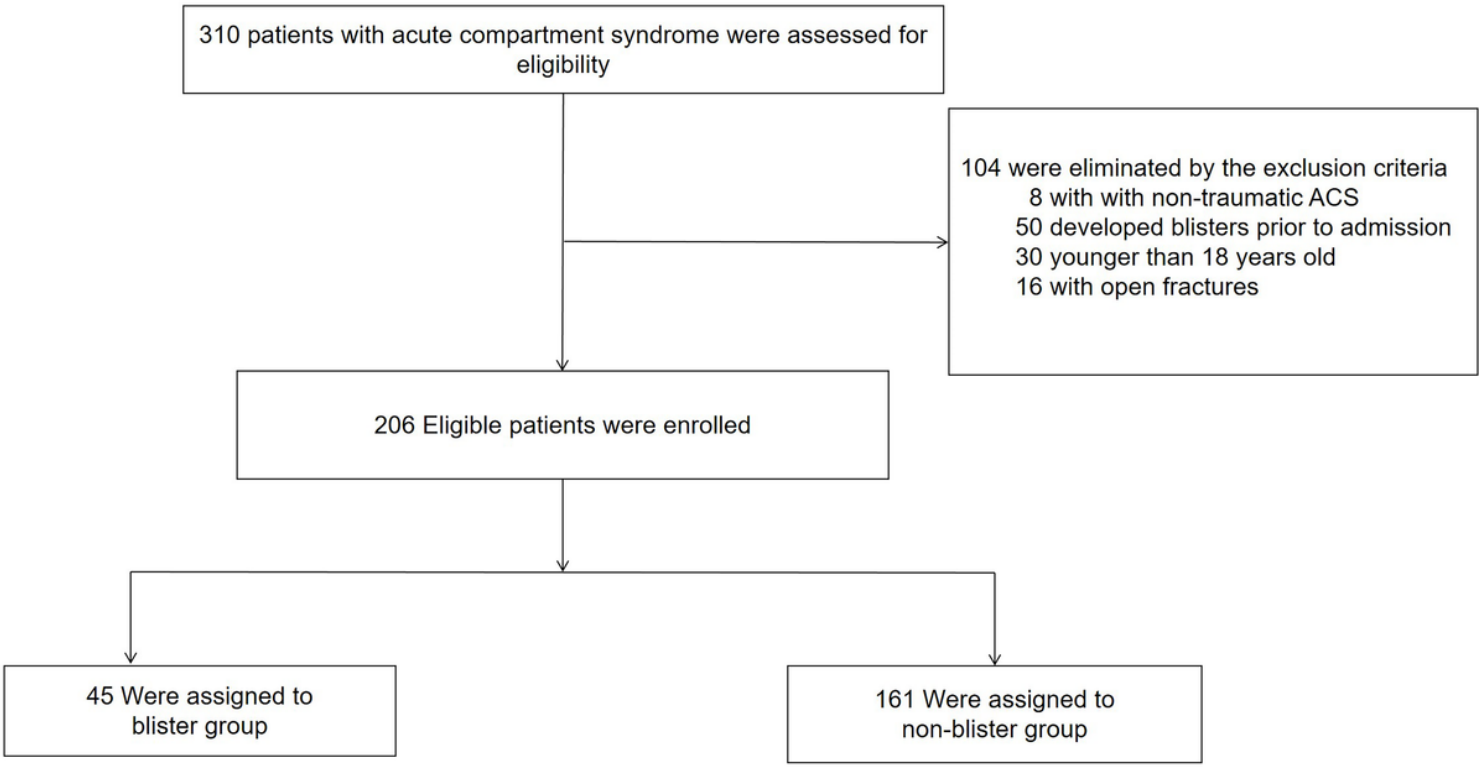

Figure 1

Legend not included with this version.

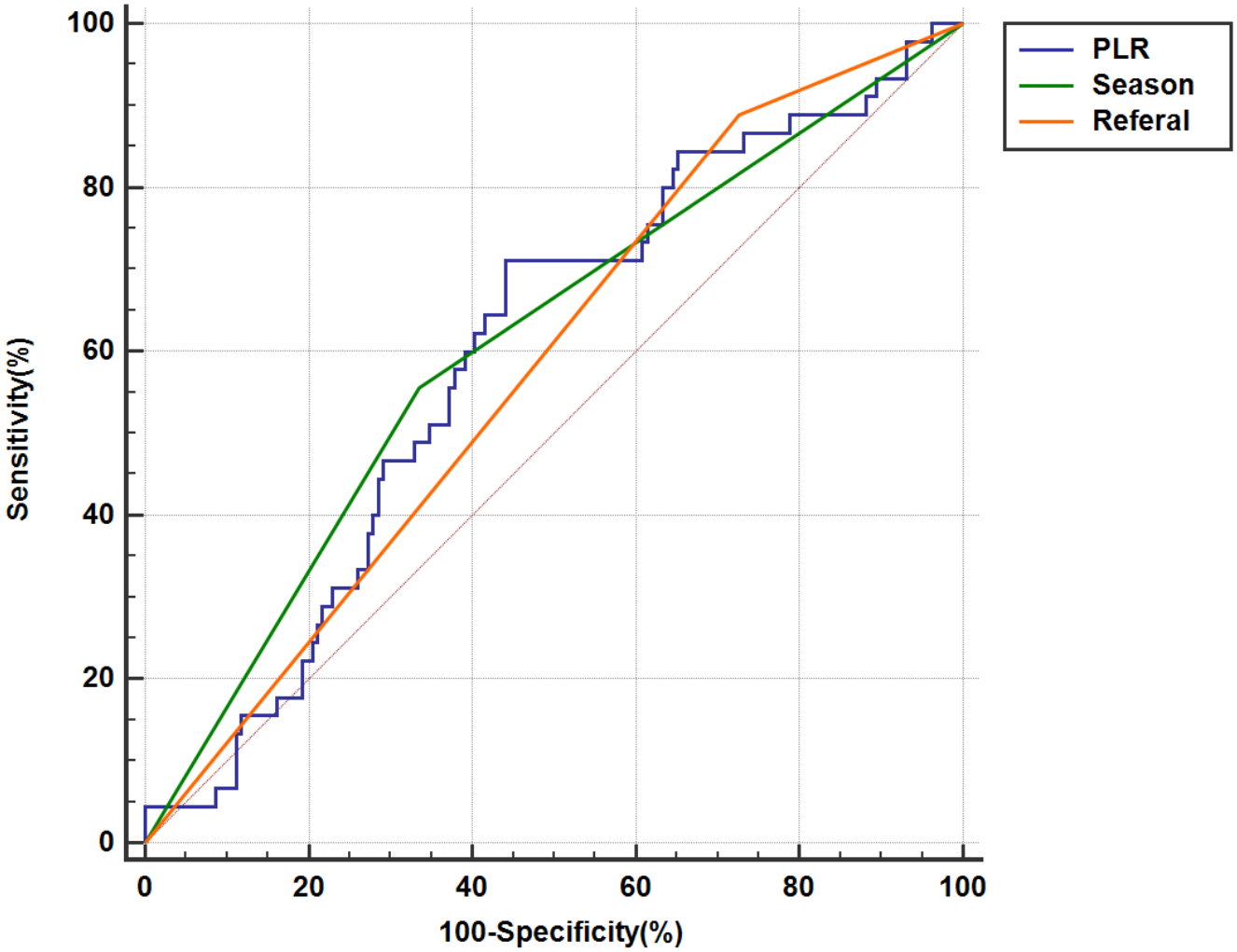

Figure 2

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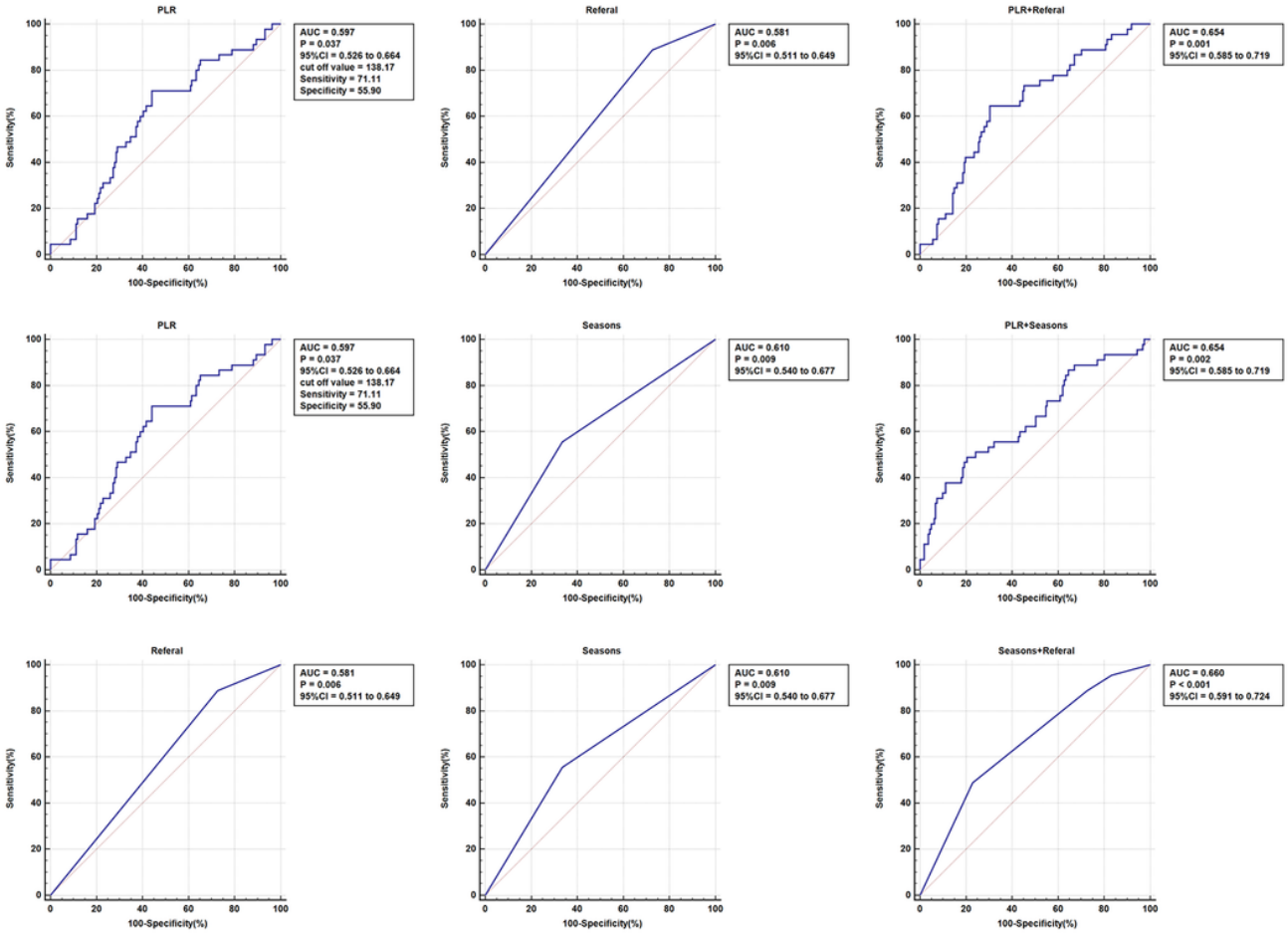

Figure 3

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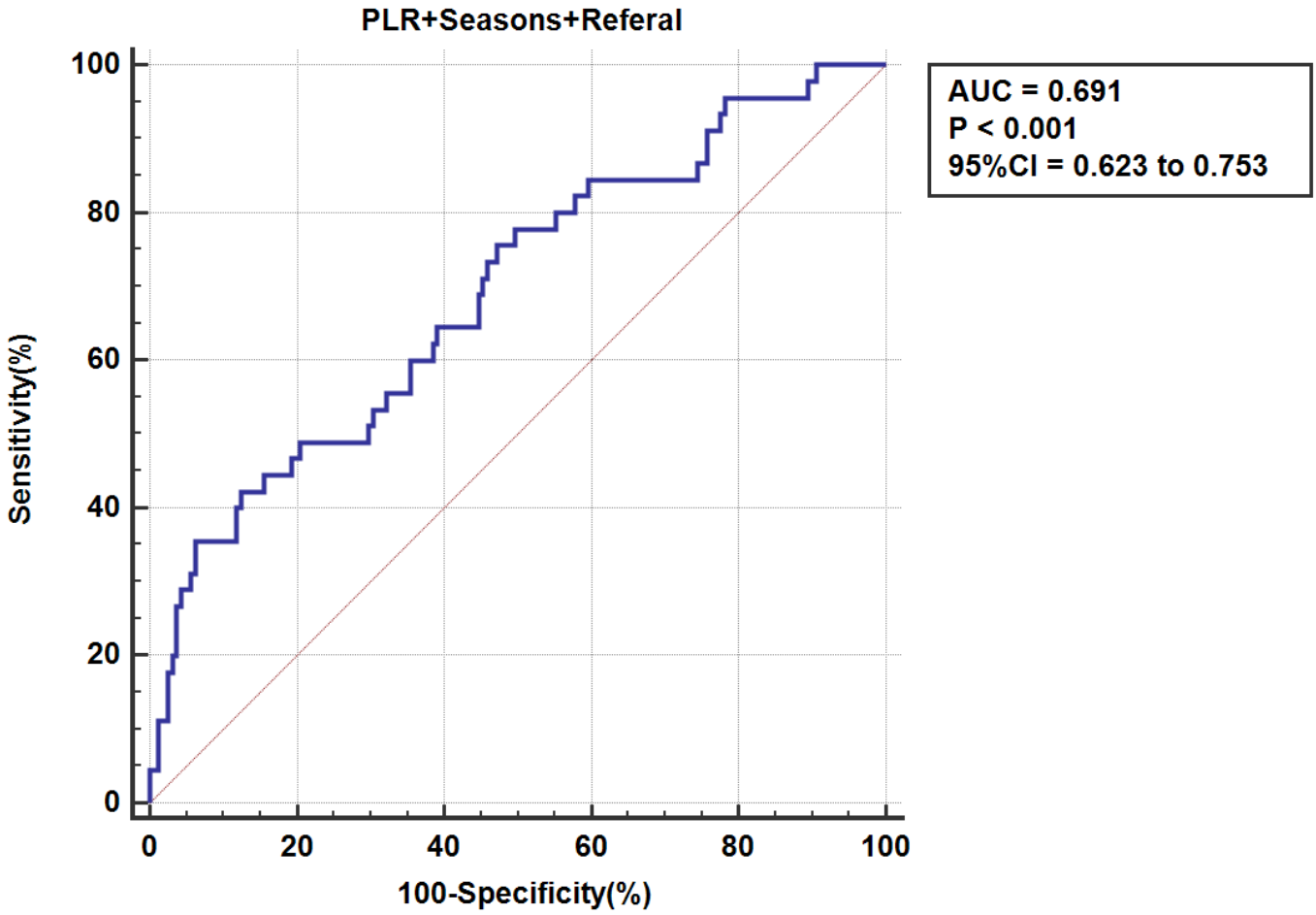

Figure 4

Legend not included with this version.